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# Maternal Uniparental Disomy (UPD) for Chromosome 2 Discovered by Exclusion of Paternity

**Ellen Heide, K.-G. Heide, and Alexander Rodewald***

*Medical Laboratory for Haemogenetics, Kiel, Institute of Human Biology, University of Hamburg (A.R.), Hamburg, Germany*

**Serological and molecular (DNA-STR) analysis of a paternity case demonstrated exclusion of paternity of the presumptive father in two markers (ACP and Apo B, both localized on chromosome 2, region 2p25.2 and 2p23/24, respectively) in a phenotypically normal girl with a normal karyotype 46,XX (by GT-banding). The index of paternity calculated for other serological (seven erythrocyte antigens, six serum protein systems, and seven isozymes, as well as the A- and B-HLA loci) and nine DNA markers, excluding ACP and Apo B, gives a very high (virtually certain) degree of paternity for the presumptive father. Maternal uniparental disomy (UPD) for chromosome 2 was suspected. Evaluation of polymorphic DNA markers (STRs) spanning chromosome 2 of the child, mother, and presumptive father demonstrated that the girl had inherited two maternal chromosome 2 homologues, whereas alleles for markers from other chromosomes were inherited from the father in a Mendelian fashion. The girl was homoallelic for informative markers mapping to the chromosomal regions 2p23-25, but she was heteroallelic for informative markers on the long arm of chromosome 2, establishing that the maternal UPD with partial isodisomy of the short arm was caused by a meiosis I nondisjunction event with genetic recombination (chiasmata in this region 2p23-25) during oogenesis. Am. J. Med. Genet. 92:260–263, 2000.**


**KEY WORDS: UPD; maternal disomy; chromosome 2; exclusion of paternity**

## INTRODUCTION

The term "uniparental disomy" (UPD) was introduced by Engel in 1980. In UPD, diploid offspring inherit both homologues of a chromosome pair from one parent. There are a number of proposed mechanisms by which UPD might arise. Nondisjunctional events during meiosis may result in aneuploid gametes that, on fertilization, give rise to UPD in the zygote by one of three mechanisms: (1) Gamete complementation by fusion of a nullisomic gamete with a gamete disomic for the same chromosome would result in a diploid zygote; (2) in monosomy duplication, a zygote resulting from the fusion of a monosomic gamete with a nullisomic gamete would be nonviable unless the single chromosome duplicated itself, resulting in isodisomy of that chromosome; or (3) in trisomy rescue, when a disomic gamete fuses with a normal monosomic gamete the resulting zygote is trisomic. If the zygote corrects the initial trisomy by loss of the supernumerary chromosome, random loss would result in a normal zygote in two-thirds of cases, and UPD in one third. Duplication of both homologues of a parental pair in a diploid genome is called "heterodisomy." UPD may affect development if an autosomal recessive gene mutation is unmasked by autozygosity, or if the chromosome involved bears regions subject to genomic imprinting. Situations analogous to those caused by imprinting in mice [Cattanach and Kirk, 1985; Searle et al., 1989] are also evident in humans, indicating that similar imprinting mechanisms exist. From mouse studies it would be predicted that imprinting regions are present on human chromosomes 2, 5, 6, 7, 11, 15, 16, 19, 20, 21, and 22 [Engel, 1998a, 1998b; Hall, 1990; James et al., 1994]. Relatively many cases of UPD in humans have been described. Pairs derived from a single parent, observed to date in one to several cases, include maternal chromosomes 1, 2, 4, 6, 7, 9, 10, 13–16, 21, 22, and X, and paternal chromosomes 1, 5–8, 11, 13–16, 20–22, X, and XY [Engel, 1997, 1998a, 1998b; James et al., 1994, 1995; Ledbetter and Engel, 1995]. Relatively few cases of maternal UPD of chromosome 2 have been reported by Bernasconi et al. [1996], Hansen et al. [1997], Harrison et al. [1995], Johnston et al. [1996], Robinson et al. [1997], Shaffer et al. [1997], and Webb et al. [1996].

*Correspondence to: Prof. Alexander Rodewald, Ph.D., Institute of Human Biology, University of Hamburg, 20146 Hamburg, Germany. E-mail: fb2a001@uni-hamburg.de

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We report here a case of maternal UPD of chromosome 2 in a phenotypically and chromosomally (46,XX) normal girl detected by paternity exclusion of the presumptive father by analysis of many serological and DNA markers.

## CASE, METHODS, AND RESULTS

The proposita was a girl (3 years old; Fig. 1) born to healthy German parents. There was no history of stillbirth or malformations in either side of the family. Chromosomal analysis discovered a numerical and structural (by GT high-resolution banding) female karyotype 46,XX. Serogenetic markers were determined by routine classical methods in the following systems: ABO, RH, MNSs, Kell, P1, Duffy, and Kidd (Table I). Serum proteins (Hp, GC, C3, BF, TF, PI), isozymes (ACP, PGM1, AK, ADA, 6-PGD, ESD, and GLO), and HLA antigens of the A and B loci were also determined (Table I). An exclusion of paternity was observed in the ACP system only (gene localized in the chromosomal region 2p25.2; child BB, mother BB, and presumptive father AA). The index of paternity (PI) for the presumptive father for all serological systems without the ACP system was PI: 481.

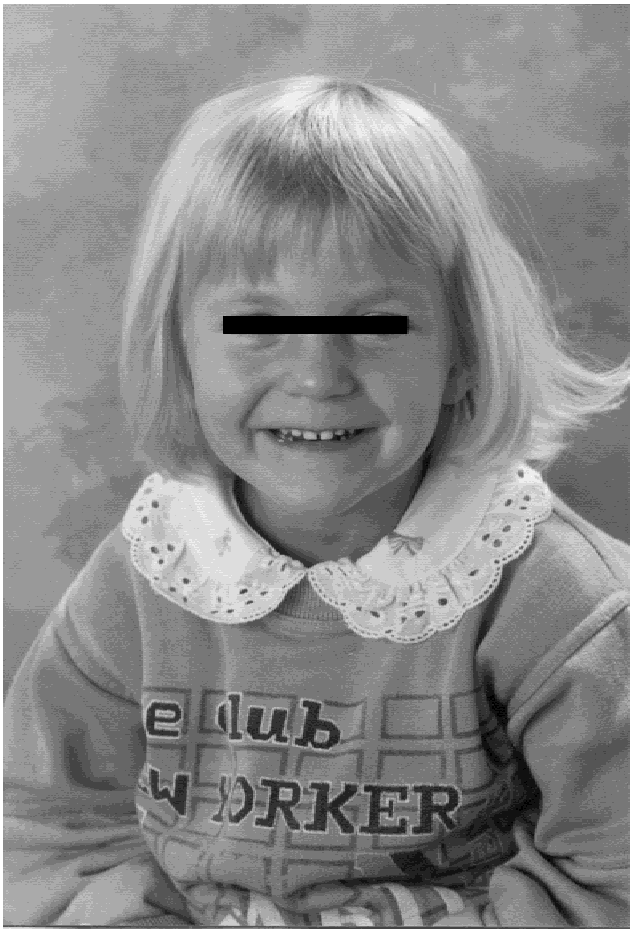


Fig. 1. The proposita with maternal disomy UPD of chromosome 2.

TABLE I. List of Serological, HLA, and DNA Markers Used for Origin of Paternity and Maternal Uniparental Disomy Analysis

| System | Child | Mother | Presumed Father |
|---|---|---|---|
| ABO | B | O | B |
| MNSs | Nss | MNss | NSs |
| Rh | ccD.Ee | CcD.Ee | CcD.ee |
| Kell | – | – | – |
| $P_1$ | + | + | + |
| Duffy (Fy) | a+ b+ | a+ b+ | a– b+ |
| Kidd (Jk) | a+ b– | a+ b– | a+ b+ |
| HP | 1–1 | 1–1 | 2–1 |
| GC | 1S | 1F–1S | 2–1S |
| C3 | SS | SS | SS |
| BF | SS | SS | SS |
| TF | C2–1 | C2–1 | C1 |
| PI | M1 | M1–Z | M1 |
| ACP | BB | BB | AA |
| PGM1 A | 1–1 | 1–1 | 3–1 |
| AK | 1–1 | 1–1 | 1–1 |
| ADA | 1–1 | 1–1 | 1–1 |
| 6-PGD | AA | AA | AA |
| EsD | 1–1 | 1–1 | 1–1 |
| GLO | 1–1 | 1–1 | 1–1 |
| HLA | $A_2$, B44/$A_1$, B8 | $A_2$, B44/$A_{24}$, B7 | $A_2$, B40/$A_1$, B8 |
| D1S80 | 18/24 | 18/22 | 24/34 |
| Apo B | 35/35 | 33/35 | 39/47 |
| D17S5 | 8/8 | 5/8 | 3/8 |
| HUMTHO1 | 6/9.3 | 7/9.3 | 6/9.3 |
| HUMvWA | 16/20 | 18/20 | 16/19 |
| FGA | 22.2/26 | 24/26 | 20/22.2 |
| hTPO | 11/11 | 11/12 | 9/11 |
| D21S11 | 30/32.2 | 27/32.2 | 30/31 |
| D18S51 | 12/18 | 15/18 | 12/14 |
| D2S162 | 130/130 | 126/130 | 126/130 |
| D2S160 | 205/207 | 205/207 | 209/211 |
| D2S168 | 153/153 | 153/167 | 153/161 |
| D2S396 | 230/236 | 230/236 | 234/234 |

### Polymorphic DNA Marker Analysis

Genomic DNA was extracted from native blood samples using a standard salting out procedure [Miller et al., 1988].

Initially, polymerase chain reation (PCR) amplifications of variable number tandem repeat (VNTR) loci D1S80, Apo B, D17S5, were performed using published conditions and primers: D1S80 with AmpliFLP™ D1S80 PCR Amplification Kit (Perkin Elmer, Weiterstadt, Germany). Apo B according to Ludwig et al. [1989] and D17S5 according to Horn et al. [1989].

PCR amplifications of the STRs were carried out with primer sequences as described for HUMTH01 [Edwards et al., 1991]; HUMvWA [Kimpton et al., 1992]; FGA [Barber et al., 1996]; hTPO [Anker et al., 1992]; D21S11 [Sharma and Litt, 1992] and D18S51 [Straub et al., 1993] (Table I).

Another exclusion of paternity was observed in the Apo B system (chromosomal region 2p23/24; child 35/35, mother 33/35, and presumptive father 39/47), on the basis of only one maternal allele (presumably present as two copies) and no paternal alleles. Subsequently, several additional STR markers spread along the short (D2S162 and D2S168-chromosomal region 2p23/24) and the long arm of chromosome 2 (D2S160-region 2q12 centromere, and D2S396 region 2q33/34)

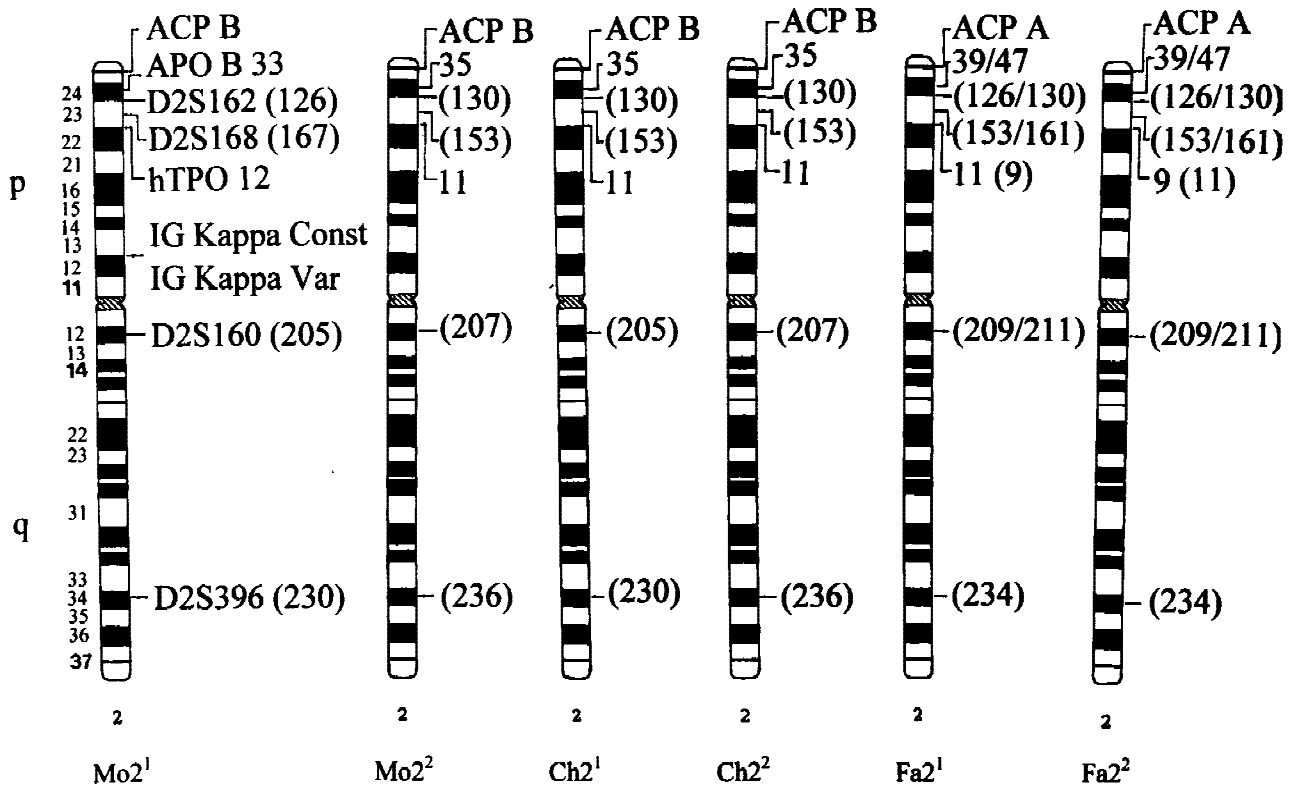


Fig. 2. Genotype analysis of the proposita (Ch = child) and her parents (Mo = mother; Fa = father) with chromosome 2 markers.

were analyzed using the primer sequences and PCR reaction conditions as described by Perkin Elmer ABI Prism™ Linkage Mapping Set, locus D2S160 Panel 3 and loci D2S162, D2S168, and D2S396 Panel 4. PCR products were analyzed via capillary electrophoresis in an ABI 310™ genetic analyzer together with an internal standard GS-350 Tamra.

As shown in Figure 2, analysis of the proposita and her parents with fully informative markers confirmed maternal UPD, and demonstrated a meiotic recombination on the short arm with chismata in the regions 2p23-pter between the two chromosomes 2 by a maternal heterodisomy. The girl was homoallelic for informative DNA markers mapping to region 2p23/24 (Apo B, hTPO, D2S162, and D2S168), but she was heteroallelic for markers mapping near the centromere (D2S160 region 2q12) and region 2q34 (D2S396).

## DISCUSSION

The occurrence of maternal UPD of chromosome 2 in the girl was shown to be the cause of the paternity exclusion of the presumptive father in the serological (ACP) and DNA markers localized on chromosome 2. On the basis of haplotype analysis, the mechanism responsible for this heterodisomic maternal UPD of chromosome 2 in the girl was maternal nondisjunction with inheritance of two chromosome 2 homologues that had recombined during meiosis I of oogenesis. Thereafter, either a nullisomic sperm for chromosome 2 fertilized a heterodisomic egg (gamete complementation), or a trisomy 2 zygote was salvaged by postfertilization loss of the paternal copy of chromosome 2 (trisomy to disomy); these two mechanisms remain theoretical explanations for this case of maternal UPD of chromosome 2.

Finally, analysis of the girl, mother, and presumptive father with several serological and DNA markers from chromosomes other than chromosome 2 showed typical Mendelian inheritance, with paternal and maternal alleles detected in the child. The index of paternity for the presumptive father for all analyzed serological and DNA markers (except ACP and Apo B) was extremely high, PI: >1,000,000, and gives virtually certain proof of paternity.

The fact that the girl was phenotypically apparently normal, as was the patient of Bernasconi et al. [1996] [certainly with two isochromosomes i(2p) and i(2q)], provides conclusive evidence that maternally derived genes on the short arm (region 2p23/24) of human chromosome 2 are not imprinted. Other patients with maternal UPD of chromosome 2, as reported previously, have had abnormal phenotypes.

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